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Melanoma Molecular Subtypes: Unifying and Paradoxical Results

Nancy E. Thomas[1], **Peter A. Kanetsky**[3], **Colin B. Begg**[4], **Kathleen Conway**[2], and **Marianne Berwick**[5]

[1] Department of Dermatology, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC

[2] Department of Epidemiology, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC

[3] Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA

[4] Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

[5] Department of Medicine, Division of Epidemiology, University of New Mexico, Albuquerque, NM

Abstract

Hacker *et al.* (in this issue) provide further evidence that molecular subtypes of malignant melanoma may develop along divergent pathways. Hacker *et al.* did not find an association between somatic *BRAF*-mutant melanoma and germline melanocortin-1 receptor (*MC1R*) gene status. We discuss this seeming paradox in light of previous studies showing strong associations.

Keywords

epidemiology; dermatology; etiology; skin pigmentation; oncogene; BRAF; MC1R; melanocortin-1 receptor; melanin; mole; nevus

Introduction

Hacker *et al.* (2009) contribute new data indicating how *BRAF*-mutant melanomas can be included (2009) in their previously proposed divergent pathway model for melanoma development. Their findings lend support to *BRAF*-mutant melanomas developing along a pathway positively associated with young age at diagnosis, high nevus counts, contiguous nevus remnants, and ability to tan and inversely associated with evidence of high level of lifetime cumulative sun exposure. However, Hacker *et al.* found no association between germline melanocortin-1 receptor *(MC1R)* status and *BRAF*-mutant melanomas in an Australian population-based study. These results differ from two earlier publications (Fargnoli *et al.*, 2008; Landi *et al.*, 2006) that reported strong associations in three independent populations (two from Italy and one from San Francisco).

Correspondence to: Nancy E. Thomas, MD, PhD, Department of Dermatology, University of North Carolina, 3100 Thurston Bowles Bldg., CB#7287, Chapel Hill, NC 27599. Phone: (919) 966-0785; Fax: (919) 966-6460; nthomas@med.unc.edu.

CONFLICT OF INTEREST

The authors state no conflict of interest.

Divergent pathways

The results of Hacker *et al.* are concordant with many other studies which have found distinct risk factors for melanomas harboring *BRAF* mutations. Both hospital and population-based studies on different continents have found *BRAF* mutations to be associated with young age at diagnosis (Edlundh-Rose *et al.*, 2006; Liu *et al.*, 2007; Thomas *et al.*, 2007). Others have reported that *BRAF*-melanomas were associated with contiguous nevus remnants on histologic sections (Edlundh-Rose *et al.*, 2006; Poynter *et al.*, 2006). Similar to Hacker *et al.*, *BRAF*-mutant melanomas have been reported to be associated with high back nevus counts and increased ability to tan in a North Carolina population-based study (Thomas *et al.*, 2007). Other studies have found *BRAF*-mutant melanomas to be inversely associated with chronically exposed anatomic site and solar elastosis, providing further evidence of an inverse association with high levels of cumulative sun exposure (Curtin *et al.*, 2005)

Paradox and possible explanations

Hacker *et al.* (2009) report no association between germline *MC1R* variants and *BRAF*-mutant melanomas in 123 cases from Australia. Similarly, we examined the relationship between *MC1R* status and *BRAF*-mutant melanomas in our North Carolina population-based study; and, similar to that of Hacker *et al.*, our results do not support a strong association.[1] In contrast, Landi *et al.* scored independent sets of 86 and 112 melanoma specimens from a case-control study in Italy and a hospital-based series in San Francisco for histologic evidence of chronic sun damage (CSD). The majority, 56 and 58, respectively, did not show CSD. They reported that *MC1R* variants were strongly associated with *BRAF*-mutant melanomas in biopsies with little histologic evidence of chronic sun damage (non-CSD) (Landi *et al.*, 2006). More recently, in a separate case-control study in Italy including 92 melanomas typed for *BRAF* mutations, Fargnoli *et al.* also found germline *MC1R* variants to be strongly associated with *BRAF*-mutations, independent of CSD status (Fargnoli *et al.*, 2008).

There are several possible explanations for the differing results among these studies. First, dissimilar estimates may be due, in part, to unique effects of specific *MC1R* variants, the frequencies of which differ somewhat among study populations. Secondly, there may be unidentified genotypic variation among populations that affects the association of *MC1R* variants with *BRAF*-mutant melanoma. For example, inherited variants in other genes related to pigmentation, tanning response, or nevus propensity might influence this association. Furthermore, environmental differences, in particular ambient sun exposure, could affect the relationship.

Gene-environment interactions involving *MC1R* could be quite complex because *MC1R* functional status alone might have opposing effects on risk of *BRAF*-mutant melanoma, as shown in Figure 1. In this model, we assume that basal pheomelanin production is the null phenotype of *MC1R* and that epidermal pheomelanin levels do not vary between the groups based on findings that *MC1R* mutations reduce eumelanin but do not change pheomelanin concentration in mouse tail epidermis (Van Raamsdonk *et al.*, 2009). Inheritance of decreased function *MC1R* variants might increase the risk of *BRAF*-mutant melanoma through diminished constitutive and facultative pigmentation, less effective DNA damage response mechanisms, and increased generation of hydrogen peroxide (Abdel-Malek *et al.*, 2008). However, carriage of more functional *MC1R* variants might increase risk because eumelanin, as well as pheomelanin, can contribute to oxidative stress (Meyskens *et al.*, 2004), and individuals with more eumelanin may increase their sun exposure due to their relatively decreased sun sensitivity.

[1]Submitted

Due to these competing effects, it is possible that genotypes with an intermediate loss of *MC1R* function might produce a favorable host phenotype for production of *BRAF*-mutant nevi and melanoma. A combination of some eumelanin and decreased DNA damage responses may be most conducive to increased risk of *BRAF* mutations. Concordant with this possibility is the finding that individuals with more than one *MC1R* red hair variants ("R/R") as defined by Duffy et al. tend to have fewer nevi (Duffy *et al.*, 2004), which frequently harbor *BRAF* mutations. In addition, patients with albinism, who have melanocytes but who do not produce eumelanin, are at low risk of developing melanoma (Ihn *et al.*, 1993). Furthermore, *MC1R* enhances repair of DNA photoproducts independent of pigmentation (Abdel-Malek *et al.*, 2008), and *MC1R* variants increase the risk of melanoma even in individuals with darker complexions, a characteristic which normally would be considered protective (Kennedy *et al.*, 2001; Palmer *et al.*, 2000).

Because all studies to date examining the association of *MC1R* variants with *BRAF*-mutant melanoma are relatively small, we cannot rule out the possibility that differing results are due to chance alone, and further investigation with larger populations will clarify the relationship. In addition, few *MC1R* "R/R" participants have been represented in the studies to date, making it difficult to assess the odds of *BRAF*-mutant melanoma in individuals with very low eumelanin levels with simultaneously decreased DNA damage responses due to their *MC1R* status. Other genes which regulate tanning responses or pigmentation might be expected to have less influence on eumelanin production in these individuals.

Increased statistical power along with ample representation of different populations, including those with different European ancestries, should help to solve this problem. This work could be approached through larger studies or meta-analyses including diverse populations. Genome-wide association and candidate pathways studies to identify and assess additional inherited melanoma risk factors should provide complementary information. Genotypic variants may be found that are associated with *BRAF*-mutations or modify the relationship between *MC1R* variants and *BRAF* mutations in melanoma. Candidate pathways of interest include those that affect pigment phenotype, tanning response, nevus propensity, and DNA damage response. An increased ability to assign inherited differences and somatic alterations in melanoma to pathways in the divergent pathway model of melanoma development should help our understanding of melanoma risk and lead to better risk prediction and targeted prevention.

Acknowledgments

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Abbreviations

MC1R	melanocortin-1 receptor

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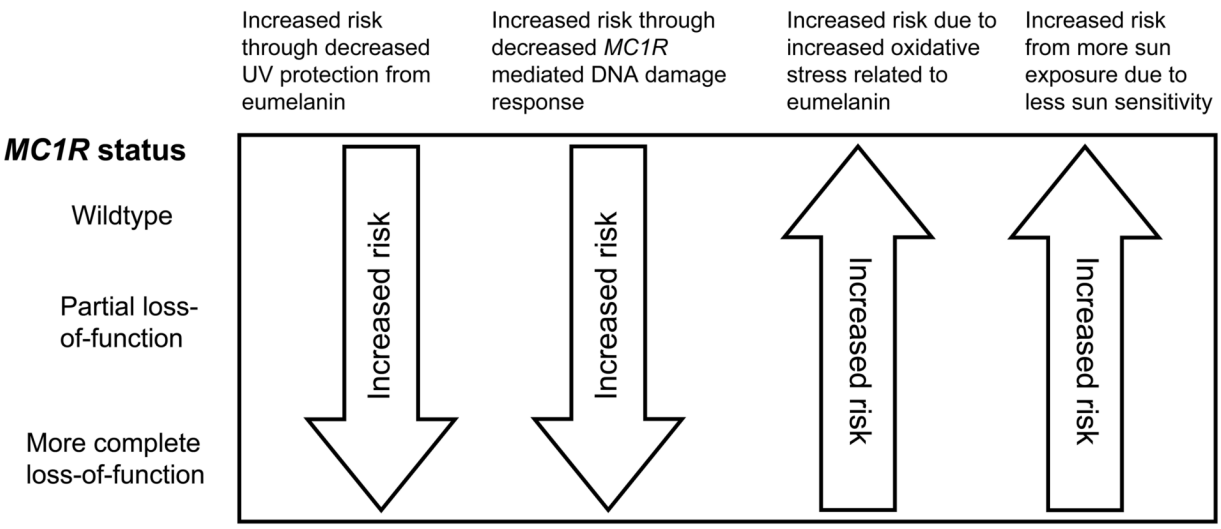

Figure 1. Potential opposing effects of *MC1R* variant status upon risk of *BRAF*-mutant melanoma

Functional *MC1R* allows the production of the darker eumelanin pigment and the tanning response. Carriage of decrease-of-function *MC1R* variants may allow increased *BRAF*-mutant melanoma risk through decreased photo-protection by eumelanin and attenuation of DNA damage response mechanisms. In opposition, more functional *MC1R* variants may increase risk through increased eumelanin leading to more oxidative stress and increase sun exposure due to less sun sensitivity.